Pulmonary Hypertension (PH)

- Sustained elevation of mean pulmonary artery pressure:
  \[ mPAP = \frac{1}{3} (PAs - PAd) + PAd \]
  Normal: 8 - 20 mmHg

Simonneau et al., J Am Coll Cardiol. 2013;62:D34-41

Objectives

- Definition and classification of pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH)
- Epidemiology and natural history
- Diagnostic approach
- Management

Disclosure

- Grants/Research Support:
  - Lung Biotechnology, Pfizer, Reata
- Consultant
  - Actelion, Gilead, Bellerophon, Cardiokinetix, Theranova/Respirex
- Speaker’s Bureau: none
- I will not discuss off-label or investigational use of drugs/devices
5th WSPH Updated Classification of Pulmonary Hypertension, Nice 2013

**GROUP 1** — **Pulmonary Arterial Hypertension**

- Idiopathic PAH
- Heritable PAH
  - BMPR2
  - ALK-1, endoglin, SMAD9, CAAV1, KCNK3
- Unknown
- Drug and toxin-induced PAH
  - Associated with: Connective tissue disease
  - HIV infection
  - Portal hypertension
  - Congenital heart disease
  - Schistosomiasis
- Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis
- Persistent PH of the newborn

**GROUP 2** — **PH Due to Left Heart Disease**

- Left Ventricular Systolic Dysfunction
- Left Ventricular Diastolic Dysfunction
- Valvular Disease
- Congenital/Acquired Left Heart Inflow/Outflow Tract Obstruction and Congenital Cardiomyopathies

**GROUP 3** — **PH Due to Lung Disease and/or Hypoxia**

- Chronic Obstructive Pulmonary Disease
- Interstitial Lung Disease
- Other Pulmonary Diseases With Mixed Restrictive and Obstructive Pattern
- Sleep-disordered Breathing
- Alveolar Hypoventilation Disorders
- Chronic Exposure to High Altitude
- Developmental Lung Diseases

**GROUP 4** — **Chronic Thromboembolic PH (CTEPH)**

**GROUP 5** — **PH With Unclear Multifactorial Mechanisms**

- Hematologic Disorders: Chronic Hemolytic Anemia, Myeloproliferative Disorders, Splenectomy
- Systemic Disorders: Sarcoidosis, Pulmonary Histiocytosis, Lymphangioleiomyomatosis
- Metabolic Disorders: Glycogen Storage Disease, Gaucher Disease, Thyroid Disorders
- Others: Tumoral Obstruction, Fibrosing Mediastinitis, Chronic Renal Failure, Segmental PH

**Etiology of PH on Echocardiogram**

- Single center study from Australia
- 6,994 screened → 936 (9.1%) with PH on ECHO (defined as ePASP >40 mmHg)

**5th WSPH Clinical Classification of PAH (WHO Group 1)**

**Group 1** — **Pulmonary Arterial Hypertension (PAH)**

- Idiopathic PAH
- Heritable PAH
  - BMPR2
  - ALK-1, endoglin, SMAD9, CAAV1, KCNK3
- Unknown
- Drug and toxin-induced PAH associated with: Connective tissue disease
- HIV infection
- Portal hypertension
- Congenital heart disease
- Schistosomiasis
- Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis
- Persistent PH of the newborn

**Group 1: Pulmonary Arterial Hypertension (PAH)**

- Subset of PH (15 cases/ million)
- US prevalence 50-100,000
- 15 – 25,000 dx & rx
- Vasoconstriction, remodeling, thrombosis in situ
- Progressive cardiopulmonary deterioration
- Leads to RH failure and death (67% 5-yr survival)

- Characterized by progressive and sustained elevation of pulmonary artery pressure and vascular resistance:
  - PA mean > 25 mmHg (nl 8-20 mmHg)
  - PAWP/LVEDP 15 mmHg (nl 4-12 mmHg)
  - PVR > 3 W units (240 dyn/sec/cm-5)

**Evaluation**

**REVEAL Database:** Most Frequent Symptoms at Diagnosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>IPAH</th>
<th>APAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea at rest</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Cough</td>
<td>16%</td>
<td>19%</td>
</tr>
<tr>
<td>Dizzy/lighthead</td>
<td>17%</td>
<td>12%</td>
</tr>
<tr>
<td>Presyncope/syncope</td>
<td>9%</td>
<td>23%</td>
</tr>
<tr>
<td>Edema</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Chest pain/discomfort</td>
<td>22%</td>
<td>20%</td>
</tr>
<tr>
<td>Other</td>
<td>22%</td>
<td>20%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19%</td>
<td>15%</td>
</tr>
<tr>
<td>Dyspnea on exertion</td>
<td>83%</td>
<td>29%</td>
</tr>
</tbody>
</table>

**Incidence (%)**


**PAH Diagnostic Guidelines: Decision Analysis**

Unexplained Symptoms of Dyspnea on Exertion, Syncope/Near Syncope, Fatigue

Clinical History, Examination, ECG, Chest X-Ray

**Signs on Physical Examination**

- Loud pulmonic valve closure ($P_2$) (93%)
- TR murmur (40%)
- PR murmur (13%)
- Right-sided fourth heart sound
- Right ventricular lift
- Jugular venous distension
- RV third heart sound (23%)
- Peripheral edema (32%)
- Ascites
- Low BP, low PP, cool extremities (low CO, peripheral vasoconstriction, hypoperfusion)
- Stigmata of associated causes of PAH

McLaughlin VV et al. JACC. 2009;53:1573-1619


Electrocardiogram

- Insufficiently sensitive as screening tool for PH
- Prognosis: p-wave in II, qR V1, RVH → risk of death
- RAD, RAE, RBBB, RVH

Chest Radiograph in PAH

- Cardiac enlargement
- Prominent proximal PA s
- "Pruning" of distal PA s
- No evidence of pulmonary edema
- Lungs appear normal

PAH Diagnostic Guidelines: Decision Analysis

- Clinical History, Examination, Chest X-Ray, ECG
- Is There a Reason to Suspect PH?
  - Yes
  - No
- Echocardiography
  - Work-Up for Other Conditions

Apical Four Chamber

- RV
- LV
- RA

Parasternal Short Axis

- RV
- LV

Normal

PAH

**Signs of PAH with Echo/Doppler**

- Increased sPAP or TR jet
- Right atrial and ventricular hypertrophy/enlargement
- Flattening of intraventricular septum
- Tricuspid regurgitation
- Small LV dimension

Traditional ECHO does not accurately measure:
- Mean PA pressure
- PAWP
- Cardiac output (blood flow)
- Cannot calculate PVR
- Other limitations - 15% no TR jet, not all congenital lesions obvious, small errors in TRV tracing can alter results

**RV function: Tricuspid Annular Plane Systolic Excursion**

- Contraction of RV is mainly longitudinal; tricuspid annulus displaced toward apex during systole
- Imaging through lateral wall with M-mode to measure this motion known as tricuspid annular plane systolic excursion (TAPSE)
- Less displacement as RV becomes more dysfunctional
- Baseline TAPSE <1.8 cm has negative prognostic implications

**PAH Diagnostic Guidelines**

**Echocardiography Indicates PH**

- Evaluate for Associated Causes
  - HIV Infection, Scleroderma, SLE, Other CTD, Liver Disease, CHD, Drug-Associated
- V/Q scan
- PFTs
- Arterial Saturation
- Suspected Chronic PE
- Parenchymal Lung Disease, Hypoxemia, or Sleep Disorder

**PAH Diagnostic Guidelines**

**Echocardiography Indicates PH**

- Evaluate for Associated Causes
  - HIV Infection, Scleroderma, SLE, Other CTD, Liver Disease, CHD, Drug-Associated
- V/Q scan
- PFTs
- Arterial Saturation
- Suspected Chronic PE
- Parenchymal Lung Disease, Hypoxemia, or Sleep Disorder
Ventilation Perfusion Lung Scan
- 3–4% of acute PE do not entirely resolve
- 50% of those with CTEPH do not have hx of acute PE
- V/Q scan is sensitive, should be performed to exclude CTEPH when another explanation for PH is present
- CTEPH: >1 segmental-sized or larger mismatched perfusion defects
- Normal or very low probability V/Q scan excludes CTEPH

<table>
<thead>
<tr>
<th>Idiopathic PAH</th>
<th>Chronic PE</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="perfusion1.png" alt="Perfusion" /></td>
<td><img src="perfusion2.png" alt="Perfusion" /></td>
</tr>
<tr>
<td><img src="ventilation1.png" alt="Ventilation" /></td>
<td><img src="ventilation2.png" alt="Ventilation" /></td>
</tr>
</tbody>
</table>

CTEPH: A “Curable” Form of PH Not to Be Missed

PAH Diagnostic Guidelines

- Echocardiography Indicates PH
- Evaluate for Associated Causes
  - HIV Infection, Scleroderma, SLE, Other CTD, Liver Disease, CHD, Drug-Associated
- V/Q scan
- Suspected Chronic PE
- Parenchymal Lung Disease, Hypoxemia, or Sleep Disorder
- Findings suggestive of PAH
  - $\downarrow$ DLCO 40% - 80% of expected
  - Mild to moderate $\downarrow$ of lung volumes
  - Peripheral airway obstruction
  - Arterial $O_2$ tension normal or slightly $\downarrow$ at rest
  - Arterial $CO_2$ is $\downarrow$
  - $SpO_2$ preserved at rest, may be $\downarrow$ with exercise/ambulation

Pulmonary Function Tests, Arterial Blood Gases, and Oxygen Saturation

- Findings suggestive of alternate PH diagnoses
  - Hypoxic PH due to COPD
    - Irreversible airway obstruction + increased residual volumes
    - reduced DLCO + normal or increased $CO_2$ tension
  - Interstitial lung disease
    - Decrease in lung volume +
    - Decreased DLCO


Echocardiography Indicates PH

**PAH Diagnostic Guidelines: Confirmation of PAH**

**Echocardiography Indicates PH**

**Right Heart Catheterization**
- Establish diagnosis
- Ascertain etiology
- Establish severity & prognosis
- Verify presence and severity of shunts
- Evaluate vasoreactivity
- Guide treatment

**PH Hemodynamic Profiles:**

*Where is the lesion? (mean PAP > 25 mmHg)*

- **Isolated post-capillary** (Passive PH)
- **Pre-capillary PH**
- **Combined post- & pre-capillary PH** (Mixed PH)
- **High flow PH**

**Algorithm for Assessment of Vasoreactivity in Patients with PAH**

**Right Heart Catheterization With Acute Vasoreactivity Testing**

(iNO, epoprostenol, adenosine)

- **mPA < 10 mmHg**
- **mPA < 40 mmHg**
- **No nCO**

- **Responder (<15%)**
  - Consider: Hemodynamically-Monitored Trial of Calcium Channel Blocker (<10% respond long-term)

- **Non-responder**
  - Consider: Oral ERAs/PDEI-5/sGCS/IPA
  - Inhaled iloprost
  - SQ/IV/inhaled/PO Treprostinil
  - IV Epoprostenol

**PAH Diagnostic Workup**

*Right Heart Catheterization Confirms PAH*

- 6-minute walk
- Borg score
- NYHA/WHO functional class

Establish Baseline, Prognosis, and Document Progression/Response to Treatment With Serial Re-assessment

---


Vachiery JL et al, J Am Coll Cardiol 2013;62: D100-8
Fang J et al, J Heart Lung Transplant 2012;31:913–33
Goals of Management of PAH
Prevent right heart failure

- Alleviate symptoms
- Improve exercise capacity
- Improve functional class
- Improve hemodynamics
- Prevent clinical worsening
- Reduce morbidity, mortality

Therapeutic Targets for PAH

Overview: 2013 WSPH Treatment Algorithm

General Measures and Supportive Therapy

Oral Anticoagulants
- IFNAH, inhaled PAH
- monoxigen induced PAH
- APAH
- Intravenous Oxygen
- Dopamine (controversial)

Acute Vasoreactivity Testing

Oral Anticoagulants
- IFNAH, inhaled PAH
- monoxigen induced PAH
- APAH
- Intravenous Oxygen
- Dopamine (controversial)

Vasoreactive

WHO-FC I-II
- CCB
- Continue CCB

Non-Vasoreactive

WHO-FC III-IV
- CCB
- Continue CCB

Initial Therapy With PAH Approved Drugs Depending on WHO-FC Status and risk profile


Adapted from Galié N et al. JACC. 2013;62(Suppl. D):D60-D72.
FDA-Approved Specific Therapies for PAH

<table>
<thead>
<tr>
<th>Class of Agent</th>
<th>Name</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin Receptor Antagonist</td>
<td>Ambrisentan</td>
<td>✔ Oral, Inhaled, IV/SC</td>
</tr>
<tr>
<td></td>
<td>Bosentan</td>
<td>✔ Oral, Inhaled, IV/SC</td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>✔ Oral, Inhaled, IV/SC</td>
</tr>
<tr>
<td>Phosphodiesterase Type 5 Inhibitor</td>
<td>Sildenafil</td>
<td>✔ Oral, Inhaled, IV/SC</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>✔ Oral, Inhaled, IV/SC</td>
</tr>
<tr>
<td>Soluble Guanylate Cyclase Stimulator</td>
<td>Riociguat</td>
<td>✔ Oral, Inhaled, IV/SC</td>
</tr>
<tr>
<td>Prostacyclin Receptor Agonist</td>
<td>Selexipag</td>
<td>✔ Oral, Inhaled, IV/SC</td>
</tr>
<tr>
<td>Prostacyclin analog</td>
<td>Epoprostenol</td>
<td>✔ Oral, IV/SC</td>
</tr>
<tr>
<td></td>
<td>Iloprost</td>
<td>✔ Oral, IV/SC</td>
</tr>
<tr>
<td></td>
<td>Treprostinil</td>
<td>✔ Oral, IV/SC, IV and SC</td>
</tr>
</tbody>
</table>


2015 ESC/ERS Guidelines: Treatment Algorithm for PAH-specific Therapy

Low or intermediate risk (WHO FC II-III)
- Initial monotherapy*
  - Inadequate clinical response
  - Double or triple sequential combination

High risk (WHO FC IV)
- Initial oral combination
  - Inadequate clinical response
  - Consider referral for lung transplantation
- Initial combination including iv prostanoids

Patient already on treatment
- Inadequate clinical response
  - Consider listing for lung transplantation

*Initial combination with ambrisentan plus tadalafil has proven to be superior to monotherapy in delaying clinical failure.

5th WSPH: Prognostic Variables Used in Clinical Practice To Set Treatment Goals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recommended Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Functional class</td>
<td>I or II</td>
</tr>
<tr>
<td>Echocardiography/CMR</td>
<td>Normal/near normal RV size and function</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>Normalization of RV function</td>
</tr>
<tr>
<td></td>
<td>-RAP &lt; 8 mm Hg and</td>
</tr>
<tr>
<td></td>
<td>-CI &gt; 2.5 to 3.0 L/min/m²</td>
</tr>
<tr>
<td>6 Minute walk distance</td>
<td>&gt;380-440 m (or more in younger pts)</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO2 &gt;15 mL/min/kg and EqCO2 &lt;45 L/min/min</td>
</tr>
<tr>
<td>B-type natriuretic peptide</td>
<td>Normal range</td>
</tr>
</tbody>
</table>

Inadequate Clinical Response to Initial PAH Therapy

Failure to show improvement or deterioration with monotherapy

Consider eligibility for lung transplant

Inadequate Clinical Response on Maximal Therapy?

Lung transplant (I-C)


GRIPHON: Selexipag for PAH

Primary Endpoint: Time to First Event

At baseline: 20%. PAH therapy naïve 47% on monotherapy (ERA or PDE-5i) 33% on combination therapy (ERA & PDE-5i)

Selexipag vs placebo: RR 40%
HR = 0.60; 99% CI, 0.46-0.78
P<0.0001

Selexipag Placebo


New Paradigm- AMBITION: Ambrisentan-Tadalafil

Up-front Combination Therapy

Primary Endpoint: Time to First Clinical Failure Event

Primary Analysis Set

Event-Free (%)

Time (weeks)

HR: 0.502
95% CI(0.348, 0.724)
p=0.0002

0 6 12 18 24 30 36

1 year 88.9%
2 year 79.7%
3 year 63.2%
4 year 56.1%
5 year 47.6%

Combination:

Pooled monotherapy:

Number at risk:

PAH: Summary

• PAH is a progressive disease associated with significant morbidity and mortality
• Echocardiography and right heart catheterization are the primary diagnostic modalities
• Strides made thus far in pathogenesis and pathobiology have lead to more effective therapies
• Current therapies have significant limitations and are costly
• New therapeutic agents and strategies are available and emerging